DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

MJ445N

FOOD & DRUG ADMINISTRATION
466 FERNANDEZ JUNCOS AVENUE
SAN JUAN, P.R. 00901-3223

March 9, 1999

WARNING LETTER
SJN-99-06

CERTIFIED MAIL
Return Receipt Requested

David Pallot
President
Allergan, Inc.
P.O. Box 19534
Irvine, California 92713-9534

Dear Mr. Pallot:

During an inspection of your drug manufacturing facility located at Road 345, Km. 1.5, Hormigueros, P.R. 00660 conducted from November 3 to December 22, 1998, our investigator documented on an FDA-483, Inspectional Observations form, several deviations from the Good Manufacturing Practice Regulations (Title 21, Code of Federal Regulations, Part 211). These deviations are in connection to your firm's manufacture of ophthalmic suspension, solution and ointment drug products causing these to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act, as follows:

1. Failure to follow stability testing programs established for Blephamide, sulfacetamide sodium and prednisolone acetate ophthalmic suspensions, and Bleph-10, sulfacetamide sodium ophthalmic solutions, as well as other different ophthalmic ointments, in accordance with 21 CFR 211.166(a)(1), resulting in a significant number of omitted test intervals in product stability studies, We refer you to Observations 1,2,3,5,8 & 9. For example:

a) at least 25 lots of Blephamide have shown missed test intervals for prednisolone acetate (PAC), including lot 5353CA tested only at the 0, 5 & 12 months and lots 5555BA and 5554CA tested at 16 months, 2 months beyond their expiry period;

b) at least 27 lots of Bleph-10 have shown missed test intervals, including lot 4200BA which was tested at the 20.7 month (about 3 months past the expiry period) for sodium sulfacetamide, and 4208CA which was tested only at 0,6.4,8,6, & 13.5 months intervals for benzalkonium cloride (BAK); and

c) ophthalmic ointments such as, Refresh lot 121AA (18 month expiry) tested only at 0 and 24 months and Lacri-lube lots 5582XA, 5582XB and 5583XA which were not tested at the 6 and 12 months testing stations and the 18 month interval was done at 19.2 months. Although stability testing at the time was conducted at Allergan Italy, the inspected firm has the responsibility to monitor and assure compliance to stability protocols for products manufactured at this facility.

2. Failure of the quality assurance unit to fully and adequately investigate stability out-of-specification incidents for several lots of Blephamide and Bleph-10 ophtalmic products in accordance with 21 CFR 211.20(a)(3) and 211.160 (we refer you to FDA-483 Observations 3(c), 8(a) & 8(b)). For example:

a) Blephamide lot 5328BA did not meet stability PAC assay specifications at 12 months and was retested without an investigation to justify invalidating those results. Stability data for Blethamide has shown in the past and continues to show failure to meet the prednisone acetate specification throughout its assigned expiration date. You have not conducted timely investigations to provide corrective action to particular problem lots nor a thorough assessment to document accurate failure rate data to assess the magnitude and provide solution to the quality problem.

b) Bleph-10, lot 4200BA failed stability protocol BAK perservative specifications but the results were invalidated after retest without appropriate justification, and using trend analysis to decide the acceptability of product lots and whether corrective actions against marketed lots are warranted.

Our inspection also revealed that you failed to submit NDA Field Alert reports (FARs) as required by the Food, Drug and Cosmetic Act, Section 505 (k) and 21 CFR 314.81(b)(1)(ii). Section 314.81(b)(1)(ii) requires that the applicant submit information concerning any significant chemical, physical or other changes or deterioration in the distributed product, or any failure of one or more distributed batches of the drug product to meet the specifications specified in the application. FARs were not submitted for several lots of Blephamide ophthalmic suspension which failed the prednisolone acetate assay specifications prior to expiration date, e.g., Lot 5560AA failed stability at both 11 and 14 months. Refer to observations 1, 2 & 3.

The intent of this regulation is to establish an early warning system so that significant problems associated with drug products already in the market are brought to the Agency's attention. This information enables FDA to evaluate in a timely manner, whether and what further action may be necessary to protect the public health. The regulation does not limit reporting of FARs to drug products in domestic distribution. As such, you are required to submit FARs for drug products in foreign distribution, if the drug product is the subject of an approved application.

We acknowledge receipt of your FDA-483 response letter from Jose Luis Diaz, General Manager, dated January 21, 1999. We also recognize your diligency in requesting, and having several of your officals attend, a meeting on January 13, 1999 to provide a preliminary response. Our review of your responses to the FDA-483 observations however, do not fully and adequately address our concerns as described above. The response to observations 4, 9 and 10, if fully implemented, adequately address the concerns of the investigators. Furthermore, the corrective action taken to resolve observations 11, 12 and 13 concerning withdrawal of the NDA supplements do not warrant further discussions with this office at this time.

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence with each requirement of the Good Manufacturing Practice Regulations. Federal agencies are advised of the issuance of all warning letters about drugs so that they may take this information into account when considering the award of contracts.

Please notify the San Juan District office in writing, within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of these or similar violations.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. These actions include seizure and/or injunction.

Your reply should be sent to the Food and Drug Administration, San Juan District Office, 466 Fernandez Juncos Ave., San Juan, Puerto Rico 00901-3223, Attention: Andres Toro, Compliance Officer.

Sincerely,

James Casey
Acting District Director

cc:

Jose L. Diaz Cotto
General Manager
Allergan America, Inc.
P.O. Box 60
Hormigueros, P.R. 00660